

Clinical Therapeutics

those obtained by DPS or GC-MS levels, suggesting that a fraction of Bu binds to blood cells.

Conclusion: This novel method can be applied with only 5 μ L of whole blood for routine therapeutic drug monitoring of Bu with accuracy and faster turnaround times in HSCT. Possibility of using capillary blood for dried blood sampling is under evaluation for its feasibility and accuracy to monitor Bu levels in pediatric patients.

Disclosure of Interest: None declared.

OC014—CLINICAL USEFULNESS OF THERAPEUTIC CONCENTRATION MONITORING FOR IMATINIB DOSAGE INDIVIDUALIZATION: RESULTS FROM THE RANDOMIZED CONTROLLED I-COME TRIAL

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Introduction: Imatinib trough plasma concentrations (C_{\min}) have been correlated with treatment response in chronic myeloid leukemia (CML) patients. The use of C_{\min} monitoring for optimizing imatinib dosage (therapeutic drug monitoring [TDM]) is therefore proposed for patients with unsatisfying response or tolerance ("rescue TDM"). A cycle of "routine TDM" for dosage individualization could also be beneficial to prevent unfavorable events, yet its clinical usefulness has not been evaluated. We aimed to assess prospectively whether a "routine TDM" intervention targeting imatinib C_{\min} of 1000 ng/mL (tolerance, 750–1500 ng/mL) could improve efficacy, tolerance, and persistence on treatment compared with "rescue TDM" use only.

Patients (or Materials) and Methods: The Swiss Imatinib COncentration Monitoring Evaluation (I-COME) study was a multicenter randomized controlled trial (ISRCTN31181395). Adult patients in chronic or accelerated phase CML receiving imatinib ≤ 5 years were eligible. Patients were randomly (1:1) allocated to receive "routine TDM" intervention or to serve as controls with access only to "rescue TDM". All had 1-year follow-up. The primary endpoint was a combined efficacy-safety outcome (failure- and toxicity-free survival without imatinib discontinuation), analyzed in intention-to-treat.

Results: Among 56 CML recruited patients, 55 had their molecular and cytogenetic response measured. 14/27 of patients receiving "routine TDM" (52% [33%–71%]) remained event-free versus 16/28 of control patients with "rescue TDM" only (57% [39%–75%]; $P = 0.69$). In the "routine TDM" group, dosage recommendations were adopted entirely in 50% of patients (median C_{\min} at study end, 895 ng/mL; CV = 33%). These patients had fewer unfavorable events (28% [5%–52%]) compared with patients not receiving the advised dosage (77% [54%–99%]; $P = 0.03$; median C_{\min} at study end, 648 ng/mL; CV = 38%).

Conclusion: This first prospective target concentration intervention trial could not formally demonstrate a benefit of "routine TDM" of imatinib, especially due to a small patient number and limited

prescriber's adherence to dosage recommendations. Nevertheless, the patients receiving the advised dosage more often met target concentrations and the combined outcome (efficacy, tolerance, and persistence). A cycle of routine TDM could thus be favorable, at least in patients eligible for dosage adjustment. Its usefulness should, however, be further confirmed in larger trials.

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OC015—UP-TITRATION STUDY WITH PONESIMOD, A SELECTIVE S1P1 RECEPTOR MODULATOR, TO ASSESS ITS MAXIMUM TOLERATED DOSE IN HEALTHY SUBJECTS

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Introduction: Ponesimod is a selective sphingosine-1 phosphate (S_1P_1) receptor modulator currently in clinical development for multiple sclerosis and plaque psoriasis. The aim of this study was to assess the maximum tolerated dose of increasing multiple doses (3-day titration steps) of ponesimod in healthy subjects.

Patients (or Materials) and Methods: This was a single-center, double-blind, placebo-controlled, randomized, parallel-group, up-titration study in healthy male and female subjects ($n = 16$). The subjects received ascending oral doses either of ponesimod ($n = 12$) or placebo ($n = 4$) once daily for 3 days at each dose level (10 mg, 20 mg, 40 mg, 60 mg, 80 mg, 100 mg). The pharmacodynamics of ponesimod were assessed by measuring the total lymphocyte count. The safety and tolerability was evaluated by monitoring adverse events, assessing standard blood chemistry and hematology laboratory variables, 12-lead ECG recordings and telemetry, measuring of vital signs, and pulmonary function tests (PFTs).

Results: A plateau in mean lymphocyte count reduction from baseline of ~70% was reached at the 40-mg dose level. The most frequent adverse events, all of mild to moderate intensity, were chest discomfort (experienced by 58% of subjects), headache (50%), dizziness (42%), dyspnea (42%), abdominal pain (33%), and night sweats (25%). A transient decrease in heart rate was observed after administration of the first 10-mg ponesimod dose (–9 beats/min at 1.5 hours postdose [placebo, –2 beats/min]). After up-titration from 10 to 20 mg (–7 beats/min at 1.5 hours postdose [placebo, –5 beats/min]) and following up-titration to higher doses, the decrease in heart rate with ponesimod was similar to placebo, suggesting that desensitization to the heart rate effect had occurred. A dose-dependent decrease in PFTs was observed and reached a plateau with 60-mg ponesimod (maximal mean decrease of 1.24 L [–30.5%] in forced expiratory volume in 1 second [FEV₁] and 0.70 L [–13.7%] in forced vital capacity [FVC]). At the dose levels of 80 to 100 mg, several subjects reported chest discomfort and dyspnea. The effects on heart rate, lymphocytes, and PFTs were fully reversible and reached baseline values within 10 days after discontinuation of treatment.

Conclusion: Ponesimod was tolerated by subjects exposed to doses of 10 to 100 mg during the 18-day up-titration regimen. The maxi-

mum tolerated dose was approached at 80 to 100 mg due to symptoms of chest discomfort and dyspnea. These results reveal a good safety margin to the highest dose selected for Phase 3 (20 mg).

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OC016—OFF-LABEL USE AND ADVERSE EVENTS OF BIOLOGIC AGENTS IN PAEDIATRIC PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Introduction: Knowledge of adverse events (AEs) from biologic drugs used in pediatric population is limited. A recent Danish study analyzing AEs submitted to the Danish National Database indicated that off-label use of medicine in general to pediatric patients is associated with increased risk of AEs. The primary objective of the present study was to analyze the safety of off- and on-label use of biologic agents in a clinical sample of pediatric patients over a 3-year period and to identify potential risk factors associated with AEs.

Patients (or Materials) and Methods: A retrospective, longitudinal, study conducted in 1 pediatric department at Copenhagen University Hospital. Patients under the age of 18 years who received a minimum 1 treatment with a biologic agent from January 1, 2009, through December 31, 2012, were included if they had been diagnosed with juvenile idiopathic arthritis (JIA) from 2009 to 2012. AEs and off-label uses were identified by medical records review and classified according to the European Medical Agency guidelines. Multivariate logistic regression was used to investigate risk factors associated with an AE, and survival analysis was used to analyze time to an AE.

Results: 81 patients were included (65.4% females). Age ranged from 1 to 18 years (mean, 11.5 years). The 81 patients had a total of 133 courses of treatment with etanercept (49.6%), adalimumab (23.3%), infliximab (10.5%), golimumab (8.2%), tocilizumab (5.2%), and abatacept (3.0%). All patients were diagnosed with JIA (26 oligoarticular, 24 polyarticular, 2 systemic, 16 enthesitis-related JIA, and 16 JIA). Totally, 252 AEs were observed in 76% of the patients, 8 (3.2 %) of which were severe. 23.8% of the AEs had a treatment consequence (reduction in dose, treatment pause, discontinuation of treatment) in 40.7% of the patients. After 200 days, 70% of all patients had experienced an AE. Gender, off-label use, type of drug, type of JIA, comedication, and comorbidity were not associated with an increased risk of AEs. Older age and severity of illness at time of treatment were the only significant predictors of AEs ($P = 0.0134$, $P < 0.0001$). Off-label use was more likely with increasing number of treatment courses. Off-label use most often comprised of not recommended dose or indication. Time to an AE occurred did not differ with respect to type of drug or numbers of treatment courses.

Conclusion: AEs are frequent in this population of pediatric patients with juvenile idiopathic arthritis treated with biologic agents. Off-label use was frequent but not associated with an increased risk of AEs.

Disclosure of Interest: None declared.

OC017—CLINICAL AND NONINTERVENTIONAL TRIALS ASSESSMENT IN CROATIA

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Introduction: Clinical trials (CT) and noninterventional trials (NIT) in Croatia are conducted in accordance with local laws (Drug law, and specific acts), and CT legislation is in accordance with European legislation. The Ministry of Health gives a final regulatory approval for CT. Since 2004, all clinical trials in Croatia have had to be reviewed by the Central Ethics Committee (CEC) and a favorable opinion must be issued before a clinical trial commences. Since December 2007, the CEC has also been responsible for issuing opinions on noninterventional trials. During the trial evaluation procedure, CEC assesses scientific and ethical considerations of the trial. The aim of this analysis is to present the procedure of central evaluation and statistics of the CEC.

Patients (or Materials) and Methods: The database of the CEC is analyzed, and the trials are presented according to indication (topic), phase, and opinion issued after the first evaluation.

Results: According to a defined procedure and discussion, the CEC positive opinion has been given to 702 CT (since May 2004–2012). During the last 5 years, 80 CT per year on average have had a positive opinion from the CEC. The greatest number of CT have been in the field of oncology (147), mental and behavioural disorders (95), and endocrine, nutritional, and metabolic diseases (88), and mostly Phase III trials. During the period of the last 5 years, CEC assessed 67 NIT. The decisions after the first evaluation were conditionally positive or postponed opinion.

Conclusion: The model of centralized CT assessment through the Central Ethics Committee, as an independent body, has been confirmed during the investigated period as appropriate for Croatia. Furthermore, CEC assessment of NIT has also been confirmed as useful because this procedure, as a gatekeeper, prevents conducting the trials only for marketing purposes and allows in Croatia only NIT of certain quality and scientific merit.

Disclosure of Interest: None declared.

OC018—THE NUMBER OF INCLUDED OLDER PEOPLE IN RECENT PRE-AUTHORISATION TRIALS

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Introduction: Older people have often been excluded from preauthorization trials. Therefore, the regulatory ICH E7 guideline requires a minimal number of older subjects for trials regarding diseases primarily related to aging (>50% of database aged 65+) and for diseases not typical for, but present in old age (>100 subjects 65+). The study objective was to analyze the number of older people in trials of recently authorized drugs indicated for diseases that regularly present in old age.

Patients (or Materials) and Methods: Eligible drugs for this descriptive study were registered by the European Medicines Agency between 2008 and 2011. Chosen indications: prevention of venous thromboembolism after replacement arthroplasty (dabigatran, rivaroxaban), osteoporosis (lasofofenone, bazedoxifene, denosumab), atrial fibrillation (dronedrone, vernakalant), diabetes mellitus type